Calcium Channel Antagonists

Pharmacology

Calcium channel antagonists (CCAs) are characterized by their chemical structure, which confers selectivity regarding tissue binding and clinical effects of toxicity. At therapeutic concentrations, organic CCAs bind to the α-subunit of the L-type calcium channel, causing the channel to favor the closed state, thereby decreasing calcium entry during phase II depolarization. At very high concentrations, some CCAs (verapamil) may occupy the channel and prevent calcium from entering the L-channel altogether. In general, however, the term *antagonist* is more accurate than *blocker* for these drugs.

Pharmacokinetics of Long-Acting Preparations

several management guidelines can be asserted for overdose of any long-acting CCA preparation: (1) If significant toxicity occurs, it will initially manifest within 6 hours of overdose (although a 12-hour delay in overt toxicity after a sustained-release verapamil overdose treated with charcoal administration has been reported); (2) peak drug levels and associated toxicity will occur within 12 hours of overdose; and (3) chronic use of the drug will worsen and prolong toxicity.

Pathophysiology

An increase in intracellular calcium causes smooth and cardiac muscle to contract and accelerates impulse formation in cardiac pacemaker cells. Conversely, a deprivation of intracellular calcium causes smooth muscle relaxation, a decrease in cardiac contraction, and a slowing of automaticity. Clinically, these effects are recognized as hypotension, bradycardia, and shock.

Verapamil is the most potent negative inotropy of all CCAs, causing equal depression of heart contraction and increase in smooth muscle dilation at any concentration. Because these effects are often undesirable in humans, dihydropyridines were developed to selectively relax smooth muscle at concentrations that produce less negative inotropy. The dihydropyridine molecule was chemically modified to yield drugs with remarkable selectivity

for vascular smooth muscle relaxation at therapeutic concentrations. Further modifications of the dihydropyridine structure led to the development of second-generation drugs that are more lipids soluble and have longer duration of action (amlodipine, in particular). These drugs appear to cause a more gradual smooth muscle relaxation, producing less reflex baroreceptor activation and less reflex tachycardia than is observed with first-generation dihydropyridines.

Clinical Presentations

As described earlier, CCAs generally produce hypotension with a slow heart rate. In most cases, CCAs produce bradycardia by decreasing sinus node firing, leading to sinus arrest, with an "escape rhythm" originating from the atrioventricular node or from a ventricular focus. Patients with severe CCA poisoning typically manifest heart rates of 45 to 55 beats per minute with no evidence of sinus node depolarization on a surface electrocardiogram (ECG). CCAs cause a decrease in systemic vascular resistance at all degrees of toxicity. Dihydropyridines are well recognized to produce reflex increases in heart rate with an increase in left ventricular stroke volume, leading to an increase in cardiac output at therapeutic and moderate toxic doses. Preliminary reports suggest that all CCAs can increase cardiac output in nonfatal overdoses. This finding has been experimentally verified in healthy animals as well and has been attributed to physiologic reflexes and neurohumoral adaptations. With severe overdose, all CCAs exert a negative inotropic effect with depressed cardiac contraction, conduction block, and hypotension with shock. Importantly, the physiologic reflexes that can preserve heart function in healthy young patients; may be inoperative in patients with preexisting cardiomyopathy, coronary artery disease, or in the elderly. Perhaps the greatest challenge to the clinician is to recognize early which patients will develop refractory cardiogenic shock after CCA overdose.

Other clinical manifestations of CCA toxicity stem from organ hypoperfusion and inhibition of metabolic processes, and these may herald the onset of shock. Many patients provide inaccurate details regarding the time and amount of ingestion; therefore, the physical examination may provide the best initial evidence of incipient–severe toxicity. Most patients with significant toxicity are drowsy asthenic. However, muscular weakness does not occur from a direct effect of CCAs on skeletal muscle excitation contraction even with massive overdoses. Mental function is often altered,

with behavior ranging from agitation to coma. With shock, cerebral hypoperfusion can cause seizure activity or stroke. Pulmonary edema frequently complicates CCA overdose, sometimes with a normal pulmonary capillary wedge pressure. Hypoxemia has also been reported, presumably from intrapulmonary ventilation-perfusion mismatch. Metabolic acidosis with hyperglycemia has been described frequently after CCA poisoning and may help differentiate CCA toxicity from toxicity from other drug ingestions. The mechanism of hyperglycemia is likely related to a suppressive effect of CCAs on pancreatic beta cell insulin release coupled with whole-body insulin resistance.

LABORATORY STUDIES

In a patient presenting with a suspected or confirmed CCA overdose, key diagnostic studies include an ECG and venous blood drawing for electrolyte and renal function determinations. In the symptomatic patient, serum calcium and potassium levels should be serially monitored. Hypokalemia is frequently observed but carries little prognostic meaning. However, hyperkalemia suggests severe cellular poisoning and marked negative inotropy can be expected with hyperkalemia in CCA overdose. Hypercalcemia is not caused by CCA overdose, although hypocalcemia has been reported. If a patient presents with hypotension and bradycardia, a serum digoxin level should be obtained if concomitant digoxin toxicity is suspected.

Management

Decontamination

Activated charcoal should be administered after the patient's airway is secured. In massive overdose, sustained-release preparations can form gastrointestinal concretions (with ileus), which can persist for days, rendering charcoal less useful. In this situation, whole-bowel irrigation with polyethylene glycol may accelerate removal of sustained-release CCA pill fragments. CCA elimination half-life is increased in overdose, and toxicity from massive overdose can last for days. Drug elimination can be enhanced by extracorporeal removal. Charcoal hemoperfusion can lower verapamil and diltiazem concentrations but may be less useful in nifedipine poisoning. However, the effect on clinical outcome is unknown, and extracorporeal technique is seldom used in CCA overdose.

Ensure airway protection and adequate ventilation and oxygenation, preferably via endotracheal intubation and mechanical ventilation. Charcoal. Whole bowel irrigation.
Administer a 10- to 20-mL/kg normal saline injection.
Keep arterial pH > 7.30 with hyperventilation and potassium level < 5.0 mEq/L (particularly if considering an insulin infusion).
Atropine for bradycardia. Begin electrical pacing for heart rate below 40 beats per minute with shock.
Administer 10 to 20 mg/kg of 1% calcium chloride solution. If favorable response, begin infusion at 20 mg/kg/hr (monitor ionized calcium, not to exceed two times normal baseline level).
Bolus injects 0.05 to 0.2 mg/kg glucagon. If beneficial, begin 0.1 mg/kg/hr infusion and titrate.
Consider beginning insulin/dextrose bolus/infusion at 1.0 U/kg IV bolus, followed by 1.0 U/kg/hr infusion with 40 mL 50% dextrose/hr).
Monitor glucose hourly.
Monitor potassium.
For Refractory Hypotension
Begin dopamine infusion at 10 μg/kg/min; titrate infusion.
Bolus amrinone at 750 μg/kg and begin 10 μg/kg/min infusion.
Consider intra-aortic balloon counter pulsation treatment or extracorporeal cardiopulmonary bypass

Angiotensin-Converting Enzyme Inhibitors

The ACE inhibitors are widely used in the treatment of hypertension and congestive heart failures. This class of drugs includes captopril, enalapril, fosinopril, lisinopril, ramipril. Captopril was the first agent to be developed. Overdose has been reported with captopril, enalapril, and lisinopril.

Pharmacology/Pathophysiology

Some agents in this class, including pentopril, ramipril, and enalapril, are prodrugs. The prodrugs are converted to active drug in the liver. They have an increased rate of absorption and longer duration of action than the other drugs in this class. Ingestion of food can reduce the absorption of an active drug, such as captopril, by 30 percent but has little effect on the absorption of a prodrug such as enalapril. Captopril levels peak 1 hour after ingestion. Enalapril is converted to enalaprilat, which reaches peak levels in serum 4 hours after ingestion. These drugs have poly phasic elimination kinetics. The prolonged terminal elimination phase is probably related to persistent binding of the drug to ACE. Captopril is eliminated from the body more rapidly, and ramiprolat, the active metabolite of ramipril, is eliminated more slowly, than other ACE inhibitors. The primary route of elimination for all is the kidney.

The pathophysiological effects are related to the pharmacologic mechanisms by which these drugs ameliorate hypertension. ACE inhibitors work by blocking ACE, located primarily in the pulmonary vascular endothelium, which is an important enzyme in the renin-angiotensin system. All ACE inhibitors have a common 2-methyl propranolol-L-proline moiety. This moiety binds to the active site of the ACE and prevents the conversion of angiotensin I to angiotensin II, which is the primary antihypertensive effect. Angiotensin II directly acts on blood vessels to cause vasoconstriction. Angiotensin II also stimulates aldosterone secretion, causing salt and water retention, and participates in the breakdown of bradykinin to inactive compounds. ACE inhibitor use results in accumulation of bradykinin, which may also reduce blood pressure, either by direct vasodilation or by stimulation of prostaglandin synthesis. Unlike other vasodilators, ACE inhibitors do not produce a reflex tachycardia. This is likely due to centrally mediated effects.

Angioedema is a rare, potentially life-threatening complication associated with the use of ACE inhibitors. Marked edema of the tongue can obstruct the airway, resulting in respiratory arrest. This phenomenon is mediated through the kallikrein-kinin system.

The hemodynamic response to ACE inhibitors is mediated by substances that bind to opiate receptors. Hypotension can occur with the first therapeutic dose of an ACE inhibitor, and this effect can be blocked by

naloxone administration. ACE inhibitors can cause renal damage by (1) reducing glomerular filtration pressure, (2) decreasing renal blood flow due to systemic hypotension, and (3) producing glomerulonephritis. Reduced aldosterone production can result in electrolyte abnormalities, specifically hyperkalemia, hyponatremia, and metabolic acidosis.

Clinical Presentation

Hypotension is the most common symptom after overdose. The hypotension may be profound and systolic pressures as low as 40 mmHg have been reported. Bradycardia has been described in a patient who ingested verapamil as well as enalapril. The level of consciousness may be depressed; this is likely caused either by co-ingested medications or by hypotension. A woman presented alert, with a blood pressure of 120/70 mmHg, 6 hours after an ingestion of enalapril. She developed hypotension and stupor simultaneously.

Hypotension can occur with the first therapeutic dose of an ACE inhibitor. Syncope and myocardial infarction have occurred in this setting in approximately 10 percent of patients, the systolic blood pressure drops by more than 50 mmHg. Patients with renovascular hypertension or volume depletion are at increased risk of reversible acute renal failure resulting from hypoperfusion has occurred with both drug overdose and therapeutic drug use. Hyperkalemia, hyperphosphatemia, hyponatremia, and metabolic acidosis have been described.

Angioedema has an overall incidence of 0.1 to 0.2 percent. The tongue and soft tissues of the neck are often affected, but the clinical presentation is unpredictable. Some cases resolve spontaneously or with standard therapies for allergic reactions, including antihistamines, corticosteroids, and epinephrine. Other cases may progress rapidly and not respond to therapy. A fatality has been reported. In this case, massive edema led to airway obstruction, requiring a surgical airway.

Severe hyperkalemia can occur if ACE inhibitors are taken with potassium supplements or potassium-sparing diuretics. Animal studies suggest that captopril may accentuate the respiratory depressive and analgesic properties of morphine. No clinical studies have been completed.

Treatment of Antihypertensive Toxicity

General management

Maintain airway and ventilation, serum electrolyte monitor especially sodium and potassium, Activated charcoal or hemodialysis

Hypotension

NaCl, Vasopressors

Dysrhythmias

Lidocaine, Procainamide

Naloxone